Three-year outcomes of the fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials

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Structured Summary

Background: In the primary week-48 analyses of two phase 3 studies, coformulated bictegravir, emtricitabine, and tenofovir alafenamide was noninferior to a dolutegravir-containing regimen in treatment-naïve people with HIV. We report week-144 efficacy and safety results from these studies.

Methods: We conducted two double-blind, active-controlled studies of bictegravir, emtricitabine, and tenofovir alafenamide (now in open-label extension phase). Study 1489 randomized (1:1) HLA-B*5701-negative adults without hepatitis B coinfection to receive coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg or coformulated dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg. Study 1490 randomized (1:1) adults to bictegravir, emtricitabine, and tenofovir alafenamide or dolutegravir 50 mg given with coformulated emtricitabine 200 mg and tenofovir alafenamide 25 mg. We previously reported noninferiority at the primary endpoint (proportion with plasma HIV-1 RNA <50 copies per mL at week 48 by U.S. Food and Drug Administration Snapshot algorithm); the week-144 secondary outcome was analysed in the same manner. These studies were registered with ClinicalTrials.gov (NCT02607930 and NCT02607956).

Findings: 629 participants were randomised and treated in Study 1489 and, 645 participants were randomised and treated in Study 1490. At week 144, bictegravir, emtricitabine, and tenofovir alafenamide remained noninferior to both dolutegravir-containing regimens for efficacy. In Study 1489, the proportion with plasma HIV-1 RNA <50 copies per mL was 81·5% (256 of 314) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 84·1% (265 of 315) in the dolutegravir, abacavir, and lamivudine group (difference −2·6%; 95% CI −8·5% to 3·4%). In Study 1490, the proportion with plasma HIV-1 RNA <50 copies per mL was 81·9% (262 of 320 participants) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 84·0% (273 of 325) in the dolutegravir plus emtricitabine and tenofovir alafenamide group (difference −1·9%, 95% CI: −7·8% to 3·9%). In both studies, no participant had treatment-emergent resistance to study drugs through week 144. All treatment regimens were well tolerated with additional exposure. Adverse events that led to study drug discontinuation were

reported for no participants in the bictegravir, emtricitabine, and tenofovir alafenamide vs five of 315 (2%) in the dolutegravir, abacavir, and lamivudine group (Study 1489) and six of 320 (2%) in the bictegravir, emtricitabine, and tenofovir alafenamide vs 6 of 325 (2%) in the dolutegravir plus emtricitabine and tenofovir alafenamide group (Study 1490). In Study 1489 (bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir, abacavir, and lamivudine), statistically significant differences were observed in median changes from baseline in fasting total cholesterol (14 mg/dL vs 10 mg/dL, p=0.034), direct LDL (21 mg/dL vs 14 mg/dL, p=0·004), and total cholesterol to HDL ratio (-0.1 vs -0.3, p=0.007) at week 144; no differences were observed for bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir, emtricitabine and tenofovir alafenamide groups in Study 1490. Weight gain was seen across all treatment groups in both studies with no differences in median changes from baseline in weight at week 144 for either study.

Interpretation: These long-term data support bictegravir, emtricitabine, and tenofovir alafenamide as safe, well tolerated, and durable treatment for people with HIV, with no emergent resistance.

Funding: Gilead Sciences, Inc.

Research in Context

Evidence before this study

Data with bictegravir regimens for HIV treatment extends to a maximum follow up time of 96 weeks. We searched PubMed for randomised clinical trials of bictegravir in people with HIV, with title and/or abstract search terms of “bictegravir” and “randomised” or “randomized”. We used internet search engines to identify governmental, non-governmental, and professional medical society practice guidelines relevant to bictegravir. Searches were limited to English language publications between January 1, 1997 and November 1, 2019. Our search yielded 14 publications, of which we excluded nine as they reported results from switch studies in virologically suppressed adults with HIV, meta- and/or systemic analyses, phase 1, or patent-reported outcome results. The remaining five reports summarised week-48 or -96 outcomes from three phase 2 and phase 3 studies of bictegravir, emtricitabine, and tenofovir alafenamide in treatment-naïve adults. Across these reports, bictegravir, emtricitabine, and tenofovir alafenamide was noninferior to standard-of-care regimens, including those containing dolutegravir. Bictegravir, emtricitabine, and tenofovir alafenamide had a similar renal, bone, and lipid safety profile relative to the comparators. Bictegravir, emtricitabine, and tenofovir alafenamide became a guidelines-recommended regimen for initial treatment of adults with HIV based on week-48 data and there remained a need for longer-term data to inform clinical care.

Added value of this study

The current randomised, blinded phase 3 studies provide evidence of the long-term (week 144) safety and efficacy of bictegravir, emtricitabine and tenofovir alafenamide. Compared with other guidelines-recommended treatment regimens (dolutegravir, abacavir, and lamivudine; and dolutegravir plus coformulated emtricitabine and tenofovir alafenamide), coformulated bictegravir, emtricitabine and tenofovir alafenamide demonstrated noninferior efficacy at week 144. No participants on any regimen failed with emergent resistance, further demonstrating the high barrier to resistance of the study regimens. There was less nausea and fewer drug-related adverse effects in those treated with coformulated bictegravir, emtricitabine and tenofovir alafenamide compared with those who received dolutegravir, abacavir, and lamivudine. Bone

mineral density, glomerular filtration rate, and biomarkers of renal tubular function were similar between bictegravir, emtricitabine, and tenofovir alafenamide and dolutegravir, abacavir, and lamivudine.

These studies provide evidence of the durable efficacy, continued tolerability, and no treatment-emergent resistance for participants taking bictegravir, emtricitabine, and tenofovir alafenamide.

Implications of all the available evidence

Data from these current analyses confirm findings from week-48 and -96 reports of randomised studies comparing bictegravir, emtricitabine, and tenofovir alafenamide with standard-of-care regimens, including those containing dolutegravir. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide can be administered once daily, does not require HLA B*5701 testing, and provides guideline-recommended therapy for people with HIV and with HIV/hepatitis B virus coinfection. Together these studies provide long-term efficacy and safety data to guide treatment decisions for people with HIV.

Main Text

Introduction

Integrase strand transfer inhibitors (INSTIs) anchor HIV treatment worldwide. Treatment regimens containing an INSTI and two nucleoside reverse transcriptase inhibitors (NRTIs) comprise most European, United States, and WHO guidelines-preferred regimens for the initial treatment of HIV.[1-4] Bictegravir is the most recent addition to the INSTI class and was compared to dolutegravir for initial treatment of HIV as a part of a complete 3-drug regimen in two different phase 3 randomised, double-blind, active-controlled trials. Bictegravir, coformulated with emtricitabine and tenofovir alafenamide, was compared to coformulated dolutegravir, abacavir, and lamivudine in Study 1489 and to dolutegravir plus emtricitabine and tenofovir alafenamide in Study 1490. All treatments had high efficacy; the bictegravir regimen was noninferior to either dolutegravir-containing regimen through 96 weeks. In Study 1489 where the NRTIs also differed between treatment arms, bictegravir, emtricitabine, and tenofovir alafenamide had similar bone and renal safety compared to dolutegravir, abacavir, and lamivudine but fewer treatment-related adverse events largely due to higher incidence of nausea in the dolutegravir, abacavir, lamivudine group.[5,6]

We report 144-week outcomes of these two trials to provide data on the relative efficacy and safety - including tolerability, renal, bone, and lipid outcomes - of bictegravir, emtricitabine, and tenofovir alafenamide versus two different guidelines-recommended, dolutegravir-containing regimens in treatment-naïve individuals initiating HIV therapy.

Methods

Study design and procedures

GS-US-380-1489 and GS-US-380-1490 were both randomised, double-blind, multicentre, active-controlled, noninferiority phase 3 trials. Study 1489 was conducted at 122 outpatient centres in nine countries Belgium, France, Germany, Italy, Spain, and the United Kingdom, Dominican Republic, Canada and the U.S. Study 1490 was conducted at 126 outpatient centres in 10 countries including the nine countries above and Australia. Detailed methods have been previously published.[5,6] Briefly, Study 1489 investigators enrolled treatment-naïve adults living with HIV with plasma HIV-1 RNA levels ≥500 copies per mL who were HLA-B*5701-negative, did not have hepatitis B virus, and who had estimated glomerular filtration rate (eGFR) ≥50 mL per minute (Cockcroft–Gault equation). Similarly, Study 1490 investigators enrolled treatment-naïve adults living with HIV with eGFR ≥30 mL per minute; participants with chronic hepatitis B infection were permitted to enter. Both studies required virologic resistance testing showing sensitivity to emtricitabine and tenofovir.

These studies were undertaken in accordance with the Declaration of Helsinki and were approved by central or site-specific review boards or ethics committees. All participants gave written informed consent.

Randomisation and masking

Participants were randomised (1:1) to receive a once-daily regimen of coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg or either dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg (Study 1489) or dolutegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg (Study 1490). All regimens were given without regard to food. Participants also received placebo tablets matching the alternative treatment; thus investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to treatment group. A computer-generated allocation sequence (block size 4) was created by Bracket (San Francisco, CA, U.S.). Randomisation in each study was stratified by HIV-1 RNA (≤100 000 copies per mL, >100 000 to ≤400 000 copies per mL, or >400 000

copies per mL), CD4 count (<50 cells per μL, 50 to 199 cells per μL, or ≥200 cells per μL), and region (U.S. or ex-U.S.) at screening.

Procedures

We conducted post-baseline study visits at weeks 4, 8, 12, and every 12 weeks thereafter, with masked treatment visits planned until week 144 as previously reported. Participants were given the option of participating in an open-label extension period for an additional 96 weeks (5 years of cumulative exposure). Laboratory tests included haematological analysis, serum chemistry tests, fasting lipids, CD4 cell counts, measures of renal function (eGFR in both studies; tubular proteinuria [urine albumin to creatinine ratio, retinol binding protein to creatinine ratio, β2-microglobulin to creatinine ratio] in Study 1489 only, (Covance Laboratories, Indianapolis, IN, U.S.), and HIV-1 RNA plasma level (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Baseline HIV-1 integrase genotyping was conducted by deep sequencing after randomization (Seq-IT, Kaiserslautern, Germany). Protocol-defined resistance testing (Monogram Biosciences, Inc., South San Francisco, CA, U.S.) was performed for any participant who had an HIV-1 RNA ≥50 copies per mL with a confirmed HIV-1 RNA ≥200 copies per mL, or who had an HIV-1 RNA ≥200 copies per mL at weeks 48, 96, 144 or the last visit on study drug after week 8, and who did not subsequently resuppress HIV-1 RNA while on study drug.

Safety was assessed by physical examinations, laboratory tests, 12-lead electrocardiogram, concomitant drugs, and recording of adverse events, which were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 22·0). Relatedness of adverse events to blinded study drugs was indicated by the investigator in a binary manner (yes or no).

In Study 1489, we performed dual energy x-ray absorptiometry (DXA) scans for hip and lumbar spine bone mineral density (BMD) before drug administration at baseline and then at weeks 24, 48, 96 and 144. A centralised centre blinded to treatment group assignment read all scans (BioClinica, Newtown, PA, U.S.).

Outcomes

We have previously reported the primary and secondary efficacy outcomes: the proportion of participants who had plasma HIV-1 RNA <50 copies per mL at weeks 48 and 96[5-8] as defined by the U.S. Food and Drug Administration (FDA) Snapshot algorithm.[9] Another secondary efficacy outcome was the proportion of participants who had plasma HIV-1 RNA <50 copies per mL by Snapshot algorithm at week 144.

Sensitivity analyses assessed virologic efficacy at week 144 in pre-specified subgroups of age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, geographic region, and study medication adherence. Other secondary efficacy analyses included the proportion of participants with plasma HIV-1 RNA <50 copies per mL at week 144 when imputing missing as failure (M=F) and missing as excluded (M=E), the proportion of participants with HIV-1 RNA <20 copies per mL at week 144 by the snapshot algorithm, and change in CD4 cell count from baseline at week 144.

In Study 1489, the percentage changes from baseline in hip and lumbar spine BMD were assessed as a secondary outcome at week 144. Renal safety assessments included the change from baseline in serum creatinine and eGFR at week 144 (both studies), treatment-emergent proteinuria through week 144 (both studies), and percentage changes from baseline in urine retinol binding protein to creatinine ratio, urine β2-microglobulin to creatinine ratio and urine albumin to creatinine ratio at week 144 (Study 1489 only).

Adverse event incident rates through week 144 and changes in fasting lipids at week 144 were assessed by treatment group.

Statistical analysis

For each study, we performed the week-144 efficacy analysis (proportion of participants with plasma HIV-1 RNA <50 copies per mL at week 144 [between days 967 and 1050, inclusive]) on the full analysis set (all participants who were randomised and had received at least one dose of the study drug) after enrolled participants had completed their week 144 study visit or had prematurely discontinued the study drug. Based on the normal approximation, we assessed

noninferiority with a Mantel-Haenszel stratified risk difference and its associated 95% confidence interval (CI) in virologic response rates of each study individually (Study 1489: bictegravir, emtricitabine, and tenofovir alafenamide minus dolutegravir, abacavir, and lamivudine; Study 1490: bictegravir, emtricitabine, and tenofovir alafenamide minus dolutegravir plus emtricitabine, and tenofovir alafenamide) with a prespecified noninferiority margin of -12%, based on published U.S. FDA regulatory guidance.[9] Sample size justification was based on the primary outcome.[7,8] Statistical analysis followed the methodology previously reported for the primary endpoint and included pre-specified subgroups, per-protocol analysis, the proportion of participants with plasma HIV RNA <20 copies per mL, and missing as failure (M=F) and missing as excluded (M=E) imputations. Changes from baseline in CD4 cell count at week 144 were summarised by treatment group with descriptive statistics based on the full analysis set using observed on-treatment data.

Methods for assessing baseline characteristics and safety outcomes including adverse events, BMD, renal biomarkers and fasting lipids were also previously reported. Significance testing was performed for adverse events with >5% treatment difference using Fisher exact text. A post-hoc analysis compared the changes from baseline in weight at week 144 using a two-sided Wilcoxon rank sum test.

We used SAS® Software Version 9·4 (SAS Institute Inc., Cary, NC, U.S.) for all analyses.

These studies were conducted according to protocol without substantial deviations and are registered with ClinicalTrials.gov, numbers NCT02607930 (https://clinicaltrials.gov/ct2/show/NCT02607930) and NCT02607956 (https://clinicaltrials.gov/ct2/show/NCT02607956).

Role of the funding source

Gilead Sciences funded the study, collected and analysed the data, interpreted the results, and helped to write the report. CO, ED, PES, JRA, SKG, CM, JLS, H-JS, DAW, FM, MAT, DP, DH, JF, CB, and AC enrolled participants. HM designed the study. HH and RA performed the data analyses, which were reviewed and interpreted by DB, SC, and HM. The first draft was written

by CO, SC and HM. All authors reviewed and interpreted analyses of data, contributed edits of the final report, and approved the draft manuscript. CO and HM made the decision to submit the manuscript for publication.

Results

Between November 13, 2015 and July 14, 2016, 631 participants were randomised in Study 1489 (316 to bictegravir, emtricitabine, and tenofovir alafenamide and 315 to dolutegravir, abacavir, and lamivudine) (Figure **1**). Of these, 314 received at least one dose of bictegravir, emtricitabine, and tenofovir alafenamide and 315 of dolutegravir, abacavir, and lamivudine. Between November 11, 2015 and July 15, 2016, 657 participants were randomised in Study 1490 (327 to bictegravir, emtricitabine, and tenofovir alafenamide and 330 to dolutegravir plus emtricitabine and tenofovir alafenamide) (Figure 2). A total of 320 received at least one dose of bictegravir, emtricitabine, and tenofovir alafenamide and 325 of dolutegravir plus coformulated emtricitabine and tenofovir alafenamide. Demographics and baseline characteristics were balanced between the treatment groups in both studies (Table 1).

At 144 weeks, the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide was noninferior to both dolutegravir-containing regimens as defined by the U.S. FDA Snapshot algorithm for the secondary efficacy outcome of the proportion of participants with plasma HIV-1 RNA <50 copies per mL (Table 2, Figure 3).

In Study 1489, 81·5% (256 of 314 participants) who received bictegravir, emtricitabine, and tenofovir alafenamide vs 84·1% (265 of 315) who received dolutegravir, abacavir, and lamivudine had a plasma HIV-1 RNA <50 copies per mL in the week 144 analysis window (difference −2·6%, 95% CI: −8·5% to 3·4%) (Table 2). An HIV-1 RNA ≥50 copies per mL at week 144 or at the last test while on study drug was observed in 2 (0·6%) participants in the bictegravir, emtricitabine, and tenofovir alafenamide arm and 9 (2·9%) in the dolutegravir, abacavir, and lamivudine arm, and there were no discontinuations due to lack of efficacy. A total of 17·8% (56 of 314) in the bictegravir, emtricitabine, and tenofovir alafenamide arm and 13.0% (41 of 315) in the dolutegravir, abacavir, and lamivudine arm did not have data at week 144 but their last on-study HIV-1 RNA test was <50 copies per mL. The most common reasons for missing data at week 144 were lost to follow-up and participant decision, occurring in 24 (7·6%) and 16 (5·1%) in the bictegravir, emtricitabine, and tenofovir alafenamide arm versus 16 (5·1%) and 15 (4·8%) dolutegravir, abacavir, and lamivudine arm, respectively. The prespecified per-

protocol, missing as excluded, and missing as failure analyses were consistent with results from the full analysis set showing high overall efficacy and no differences between the treatment groups (Table 2). Testing for interactions between treatment and subgroup was performed using the Wald test and identified differences between treatment arms favouring dolutegravir, abacavir, and lamivudine in the subgroup with cumulative adherence <95% (appendix page 16). The difference was driven by subgroup participants who did not have data in the analysis window and whose last on treatment assessment of HIV-1 RNA was <50 copies per mL (n=31 [30·4%] in the bictegravir, emtricitabine, and tenofovir alafenamide arm versus n=15 [12·7%] in the dolutegravir, abacavir, and lamivudine arm), rather than virologic failure (appendix page 9). No significant treatment differences were noted for other pre-specified subgroups. Results across other efficacy outcomes consistently demonstrated the durable efficacy of both regimens (Table 2). Six participants with protocol-defined criteria for resistance testing were included in the week-144 resistance analysis population; all were in the dolutegravir, abacavir, and lamivudine group. Of these, 1 participant had resistance testing between week 96 and 144. No emergent resistance developed to any component of either treatment regimen. CD4 cell count increased in each treatment group, with mean (SD) changes from baseline at week 144 of 299 (224·9) cells per μL for bictegravir, emtricitabine, and tenofovir alafenamide and 317 (219·5) cells per μL for dolutegravir, abacavir, and lamivudine (p=0·30).

In Study 1490, 81·9% (262 of 320 participants) who received bictegravir, emtricitabine, and tenofovir alafenamide vs 84·0% (273 of 325) who received dolutegravir plus emtricitabine, and tenofovir alafenamide had a plasma HIV-1 RNA <50 copies per mL in the week 144 analysis window (difference −1·9%, 95% CI: −7·8% to 3·9%) (Table 2). An HIV-1 RNA ≥50 copies per mL at week 144 or at the last test while on study drug was observed in 15 (4·7%) in the bictegravir, emtricitabine, and tenofovir alafenamide arm and 10 (3·1%) in the dolutegravir plus emtricitabine and tenofovir alafenamide arm. The majority of these (14 [4·4%) vs 6 [1·8%]) were participants who discontinued study drug due to other reasons not related to efficacy and had a last available HIV-1 RNA value ≥50 copies per mL. There were no discontinuations due to lack of efficacy. Seven participants from the bictegravir, emtricitabine, and tenofovir alafenamide arm

did not have any HIV-1 RNA data after baseline; therefore, the only available HIV-1 RNA, which was used to assess efficacy through week 144, was collected before they initiated study treatment. We observed no differences between treatment arms in the pre-specified subgroups (appendix page 17). Results across other efficacy outcomes consistently demonstrated the durable efficacy of both regimens (Table 2). Fifteen participants met criteria for viral resistance testing at week 144: eight in the bictegravir, emtricitabine, and tenofovir alafenamide group and seven in the dolutegravir plus emtricitabine and tenofovir alafenamide group. One new participant in the bictegravir, emtricitabine, and tenofovir alafenamide group and three participants in the dolutegravir plus emtricitabine and tenofovir alafenamide group had resistance testing between week 96 and 144. No emergent resistance developed to any component of either treatment regimen.

Baseline HIV-1 integrase genotyping was not required at study entry and was completed retrospectively for both studies showing that primary mutations associated with resistance to integrase inhibitors were present in 8 (1·3%) participants in Study 1489 and 9 (1·4%) in Study 1490, all but one of whom had pre-existing Thr97Ala which did not affect virologic outcomes in either study. One participant in Study 1489 who had Gln148His + Gly140Ser substitutions with phenotypic resistance to raltegravir and elvitegravir, partial resistance to dolutegravir, and full sensitivity to bictegravir, was randomised to bictegravir, emtricitabine, and tenofovir alafenamide and had HIV-1 RNA <50 copies per mL at week 4 and through week 144.

In Study 1490, 14 participants had HIV-1 and hepatitis B co-infection at baseline: eight in the bictegravir, emtricitabine, and tenofovir alafenamide group and six in the dolutegravir plus emtricitabine and tenofovir alafenamide group. At week 144, by M=E analysis 11 of 11 HIV and hepatitis B coinfected participants had HBV DNA < 29 IU per mL and HIV-1 RNA <50 copies per mL; five of five from the bictegravir, emtricitabine, and tenofovir alafenamide group and six of six from the dolutegravir, emtricitabine, and tenofovir alafenamide group. Three participants in the bictegravir, emtricitabine, and tenofovir alafenamide had HBV DNA missing at week 144; two had no HBV DNA detected at the last visit at which HBV was tested and one had no post-baseline visits. Among HIV and HBV coinfected participants there were no hepatic adverse

events, no grade 3 or 4 adverse events and no participants interrupted or discontinued their study regimen due to an adverse event.

The median study drug exposure was 152 weeks for Study 1489 and 149 weeks in Study 1490. Most adverse events were reported as mild or moderate in severity. Table 3 shows adverse events reported by 10% or more of participants in any treatment group for each study. In Study 1489, nausea was reported in significantly fewer participants in the bictegravir, emtricitabine, tenofovir alafenamide group than in the dolutegravir, abacavir, and lamivudine group (12% [38 of 314] vs 24% [76 of 315], p=0·0001). The incidence of nausea was highest after starting treatment (week 4: 5% [16 of 314] in the bictegravir, emtricitabine, and tenofovir alafenamide group vs 17% [54 of 315] in the dolutegravir, abacavir, and lamivudine group) with a difference between treatments in prevalent nausea through week 144 (appendix page 18). In each study, adverse events were similar to those reported at weeks 48 and 96. In Study 1489, few participants had adverse events that led to study drug discontinuation (0 in the in the bictegravir, emtricitabine, and tenofovir alafenamide group vs 2% [5 of 315 participants] in the dolutegravir, abacavir, and lamivudine group) (Table 3), all of which occurred before week 96. In Study 1490, adverse events leading to study drug discontinuation were also uncommon, occurring in 2% (6 of 320) of participants in the bictegravir, emtricitabine, and tenofovir alafenamide and 2% (6 of 325) in the dolutegravir plus emtricitabine and tenofovir alafenamide group (Table 3). Only one event (large B-cell lymphoma in the in the dolutegravir plus emtricitabine and tenofovir alafenamide group) led to discontinuation between weeks 96 to 144.

In Study 1489, participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had a lower incidence of drug-related adverse events than did those in the dolutegravir, abacavir, and lamivudine group (30% [94 of 314] vs 42% [132 of 315], p=0·0021) (Table 3); these events were primarily mild or moderate in severity. The difference between groups was driven mainly by the significant difference in drug-related nausea reported soon after initiation of blinded study drug, which occurred in 6% (18 of 314) bictegravir, emtricitabine, and tenofovir alafenamide group vs 18% (56 of 315) dolutegravir, abacavir, and lamivudine group (p<0·0001). The study-drug related adverse events reported in ≥2% of participants in Study 1489 are shown

on appendix page 10. In Study 1490, study-drug related adverse events were reported for 71 participants (22%) in the bictegravir, emtricitabine, and tenofovir alafenamide and 95 (29%) in the dolutegravir, emtricitabine, and tenofovir alafenamide group. Study-drug related adverse events reported in ≥2% of participants in Study 1490 are shown on appendix page 11. In Study 1490, no single adverse event (MedDRA preferred term) met the 5% threshold for between group statistical comparison. No drug-related adverse events of grade 3 or higher were reported in >2 participants in either group across both studies.

In Study 1489, two deaths occurred prior to week 96, as previously reported[5,7] (drug overdose [n=1] and suicide [n=1] in the bictegravir, emtricitabine, and tenofovir alafenamide group). One death (overdose [n=1] in the dolutegravir, abacavir, and lamivudine group) occurred after week 96. None of the deaths in Study 1489 were considered to be related to treatment. In Study 1490, eight participants died during the study, four in each group. In the bictegravir, emtricitabine, and tenofovir alafenamide group sudden cardiac death was reported in one participant after week 96, the other deaths (cardiac arrest following appendicitis and septic shock [n=1)] gastric adenocarcinoma [n=1], hypertensive heart disease and congestive cardiac failure [n=1]) occurred before week 96, as previously reported.[6,8] In the dolutegravir, emtricitabine, and tenofovir alafenamide group two deaths occurred after week 96 (unknown cause [n=1] and lymphoma [n=1]); the other deaths (unknown cause [n=1] and pulmonary embolism [n=1]) occurred prior to week 96, as previously reported.[6,8] One death in from unknown cause on Study 1490 in a participant on dolutegravir, emtricitabine and tenofovir alafenamide was considered possibly related to study treatment, none of the other deaths on either study were considered related to study treatment.

Study drugs were interrupted or discontinued by the investigator when any on-study pregnancy was confirmed. Three women in Study 1489 had confirmed pregnancies while on-study, two in the bictegravir, emtricitabine, and tenofovir alafenamide group and one in the dolutegravir, abacavir, and lamivudine group; all before week 96. The pregnancy outcomes were previously reported including a healthy full-term infant (n=1) and spontaneous abortion at 2 weeks gestation (n=1) in the bictegravir, emtricitabine, and tenofovir alafenamide group, and elective

termination (n=1) in the dolutegravir, abacavir, and lamivudine group. Ten women in Study 1490 had thirteen confirmed pregnancies, six women in the bictegravir, emtricitabine, and tenofovir alafenamide group with nine confirmed pregnancies and four women in the dolutegravir, emtricitabine, and tenofovir alafenamide group with four confirmed pregnancies. In the bictegravir, emtricitabine, and tenofovir alafenamide group, the pregnancies resulted in uncomplicated term delivery (n=3), spontaneous abortion (n=3), elective termination (n=1) and two pregnancies are ongoing. In the dolutegravir, emtricitabine, and tenofovir alafenamide group, the pregnancies resulted in uncomplicated term delivery (n=3) and elective termination (n=1). There were no reports of infant congenital abnormalities in either study.

The overall laboratory safety profiles at week 144 in both studies were similar to those observed at weeks 48 and 96. In Study 1489, grade 3 or 4 laboratory abnormalities were reported for 26% (83 of 314) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 25% (80 of 315) in the dolutegravir, abacavir, and lamivudine group (appendix page 12). In Study 1490, grade 3 or 4 laboratory abnormalities were reported for 25% (77 of 320) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 23% (74 of 325) in the dolutegravir plus coformulated emtricitabine and tenofovir alafenamide group (appendix page 13). In both studies, incidence and types of abnormalities were generally balanced between treatment groups. The majority were transient and resolved on therapy. There were no abnormal electrocardiogram findings through week 144 associated with either treatment in each study.

There were no cases of proximal tubulopathy or Fanconi syndrome reported in either study. No study participant who received bictegravir, emtricitabine, and tenofovir alafenamide in either study discontinued due to a renal adverse event; one individual in the dolutegravir, abacavir, and lamivudine group discontinued treatment in Study 1489 due to renal failure as previously reported.[5,7] Small increases from baseline in median serum creatinine and decreases in eGFR were seen at week 144 for both groups in each study (appendix page 14). At 144 weeks in Study 1489, percentage changes in quantitative proteinuria (total urinary albumin to urine creatinine ratio) and tubular proteinuria (retinol binding protein and β2-microglobulin to urine creatinine ratios) were similar between groups (appendix page 14).

In Study 1489, changes from baseline in fasting HDL and triglycerides were similar between groups at week 144 (appendix page 15). Significant differences were measured in the median changes from baseline in fasting total cholesterol (14 mg/dL vs 10 mg/dL, p=0.034), direct LDL (21 mg/dL vs 14 mg/dL, p=0·004), and total cholesterol to HDL ratio (-0.1 vs -0.3, p=0.007) at week 144 in the bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine groups. There were no differences between groups in initiation of lipid-modifying agents during the study for the bictegravir, emtricitabine and tenofovir alafenamide compared to dolutegravir, abacavir, and lamivudine groups through week 144: 5% (16 of 314) vs 5% (16 of 315) (p=1·00). No differences in median changes from baseline in fasting lipid parameters at week 144 were noted for the bictegravir, emtricitabine and tenofovir alafenamide and dolutegravir, emtricitabine and tenofovir alafenamide groups in Study 1490 (appendix page 15).

There were small changes from baseline in hip and lumbar spine BMD that were similar between the bictegravir, emtricitabine, and tenofovir alafenamide and dolutegravir, abacavir, and lamivudine groups in Study 1489. Mean percentage changes at week 144 were -1·02% vs -1·29% (p=0·39 for difference in percentage changes at week 144 between groups) at the hip and -0·37% vs +0·04% at lumbar spine (p=0·26) (Figure 4). There were similar changes from baseline in weight at week 144 in both groups in each study (appendix pages 15 and 19). In Study 1489, the median change in weight from baseline (interquartile range) was +4·1 kg (0·3, 8·7) in the bictegravir, emtricitabine, and tenofovir alafenamide group and +3·5 kg (0·0, 7·7) in the dolutegravir, abacavir, and lamivudine group (P=0.196). In Study 1490, the median change (interquartile range) was +4·4 kg (1·0, 9·0) in the bictegravir, emtricitabine, and tenofovir alafenamide group and +5·0 kg (0·5, 9·7) in the dolutegravir plus emtricitabine and tenofovir alafenamide group (P=0.649).

Discussion

Current results from these two large, randomised, phase 3 trials offer three-year data demonstrating noninferiority of coformulated bictegravir, emtricitabine, and tenofovir alafenamide to two dolutegravir-containing regimens for initial treatment of people with HIV. The proportions who remained virologically suppressed at 144 weeks were high, with similar efficacy for participants with high baseline plasma HIV-1 RNA (>100,000 copies per mL) and for those with CD4 cell counts above and below 200 cells per uL. Virologic failure was rare; no participant in either study discontinued due to a lack of efficacy and very few had plasma HIV-1 RNA >50 copies per mL at week 144. Notably, no participant in either trial had emergent drug resistance detected.

Few discontinuations of study drug due to intolerance or adverse effects were reported through 144 weeks (six of 634 participants [1%] on bictegravir, emtricitabine, and tenofovir alafenamide across both studies, five of 315 (2%) on dolutegravir, abacavir, and lamivudine, and six of 325 (2%) on dolutegravir plus emtricitabine and tenofovir alafenamide). In Study 1489, more participants (24%) treated with dolutegravir, abacavir, and lamivudine experienced nausea compared to those (12%) treated with bictegravir, emtricitabine, and tenofovir alafenamide. Though nausea most commonly occurred shortly after starting treatment, prevalence remained higher in the dolutegravir, abacavir, and lamivudine group throughout the three-year study period.

In 144 weeks of follow-up in these two large clinical trials, there were no participants who had treatment-emergent resistance detected, which underscores the high barrier to resistance for standard-of-care regimens containing either bictegravir or dolutegravir in combination with two NRTIs. A lack of emergent drug resistance is essential to the lifelong durability of HIV treatment.

Across both studies, no participant was diagnosed with proximal tubulopathy or Fanconi syndrome. As expected, given the inhibition of renal creatinine transporters by both bictegravir and dolutegravir, there were small increases from baseline in serum creatinine that occurred early. Estimated glomerular filtration remained stable in the treatment groups from week 4 through week 144 and did not show evidence of renal toxicity with longer exposure to the

treatment regimens. Similarly, in Study 1489 which included longitudinal monitoring of bone density using dual-energy x-ray absorptiometry, there were no differences in bone mineral density changes between bictegravir, emtricitabine, and tenofovir alafenamide and dolutegravir, abacavir, and lamivudine groups. Both treatments showed similar, well-described declines after antiretroviral treatment was started, reaching a nadir at week 24 for the spine before increasing towards baseline and a plateau after week 48 for measurements at the hip.

Lipids changed from baseline in all groups. Participants in Study 1489 receiving bictegravir, emtricitabine, and tenofovir alafenamide had modestly larger increases in total and direct LDL cholesterol, as well as smaller reductions in total cholesterol:HDL ratio, than those receiving dolutegravir, abacavir, and lamivudine.

Consistent with data from prior studies in treatment-naïve populations,[11-16] participants in both studies experienced weight gain. Interestingly, statistically significant differences in change in weight from baseline between the treatment groups were not observed in either study at week 144. Weight gain and obesity related morbidity and mortality among people with HIV is increasingly recognized as an emerging concern and has been associated with antiretroviral drugs and patient characteristics [11, 17-22].

Consistent with other data, a pooled analysis, which included data from Studies 1489 and 1490, showed that newer antiretroviral agents, including bictegravir, dolutegravir and tenofovir alafenamide used in this study, were consistently associated with more weight gain than older comparators and speculated that improved tolerability of treatments may be a contributing factor to differential weight gain over time.[11] The metabolic implications of the weight gain and lipid changes observed in these studies are unknown and warrant further study. Biological mechanisms that may contribute to differential weight gain on antiretroviral therapy are yet to be determined.

These studies have several limitations. Importantly, the relatively low enrolment of women and people with advanced HIV disease mean that the findings cannot be assumed to be generalizable to these populations. Given the lack of data supporting the use of bictegravir, emtricitabine and tenofovir alafenamide in pregnant women, we restricted enrolment only to

women of childbearing potential who were willing to conform to the protocol's stringent birth control requirements. An international study of 470 women with suppressed plasma HIV-1 RNA showed high rates of continued suppression after switching to bictegravir, emtricitabine, and tenofovir alafenamide with no discontinuations due to adverse events.[23] Although our results are similar, they are based on too small a sample of women to be considered definitive supportive of this finding. Given the known increased risk for weight gain in women and people with advanced HIV disease who start antiretroviral therapy, a greater degree of weight gain may be expected in a cohort with higher percentages of women and people with advanced HIV. In a pooled analysis of week 144 results for Studies 1489 and 1490, the median changes in weight for women were 5.0 kg in the bictegravir, emtricitabine, and tenofovir alafenamide group, 7.9 kg in the dolutegravir, abacavir, and lamivudine group, and 4.9 kg in the dolutegravir, emtricitabine tenofovir alafenamide group.[24]

Overall, these results demonstrate that all three regimens were efficacious and safe. In distinguishing among them, the higher rates of study-drug related adverse events and the limitations to the use of dolutegravir, abacavir, and lamivudine, including among those with hepatitis B virus co-infection and the requirement for HLA-B*5701 screening, support the use of bictegravir, emtricitabine, and tenofovir alafenamide, or alternatively dolutegravir plus emtricitabine, tenofovir alafenamide in particular patient populations.

In summary, as was observed at weeks 48 and 96, bictegravir, emtricitabine, and tenofovir alafenamide at 144 weeks of therapy continued to be noninferior to dolutegravir-containing regimens, with no emergent drug resistance or proximal renal tubulopathy detected, but with a better gastrointestinal tolerability profile. Further open-label follow-up through a total of 5 years of exposure in each study will provide further information about the safety and durable efficacy of bictegravir, emtricitabine, and tenofovir alafenamide in people with HIV.

Contributors

CO, ED, PES, JRA, SKG, CM, JLS, H-JS, DAW, FM, MAT, DP, DH, JF, CB, and AC enrolled participants. HM designed the study. HH and RA performed the data analyses, which were reviewed and interpreted by DB, SC, and HM. The first draft was written by CO, SC and HM. All authors reviewed and interpreted analyses of data, contributed edits of the final report, and approved the draft manuscript. CO and HM made the decision to submit the manuscript for publication.

Declaration of Interests

HH, RA, DB, SC, and HM are employees of Gilead Sciences and shareholders of Gilead stock. Declaration of interest for other authors are forthcoming.

Data sharing

Gilead shares anonymized Individual Patient Data (IPD) upon request or as required by law and/or regulation with qualified external researchers. Approval of such requests is at Gilead's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to: datarequest@gilead.com.

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Tables and figures

Table 1. Baseline demographic and clinical characteristics

Characteristic	Study 1489		Study 1490	
	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	Dolutegravir, abacavir, and lamivudine (n=315)	Bictegravir, emtricitabine, and tenofovir alafenamide (n=320)	Dolutegravir plus emtricitabine, and tenofovir alafenamide (n=325)
Age (years)	31 (18, 71)	32 (18, 68)	33 (18, 71)	34 (18, 77)
Women	29 (9%)	33 (10%)	40 (13%)	37 (11%)
Race				
White	180 (58%)	179 (57%)	183 (57%)	195 (60%)
Black	114 (36%)	112 (36%)	97 (30%)	100 (31%)
Asian	6 (2%)	10 (3%)	7 (2%)	10 (3%)
Ethnicity				
Hispanic or Latino	72 (23%)	65 (21%)	83 (26%)	81 (25%)
HIV Disease status				
Asymptomatic	286 (91%)	286 (91%)	286 (89%)	288 (89%)
Symptomatic	16 (5%)	14 (4%)	10 (3%)	11 (3%)
AIDS	12 (4%)	15 (5%)	24 (8%)	26 (8%)
HIV risk factor				
Heterosexual sex	61 (19%)	62 (20%)	81 (25%)	77 (24%)
Homosexual sex	251 (80%)	250 (79%)	237 (74%)	250 (77%)
Intravenous drug use	5 (2%)	4 (1%)	3 (1%)	6 (2%)
HIV-1 RNA $\log_{10}$ copies per mL	4.42 (4.03, 4.87)	4.51 (4.04, 4.87)	4.43 (3.95, 4.90)	4.45 (4.03, 4.84)
HIV-1 RNA concentration >100 000 copies per mL	53 (17%)	50 (16%)	66 (21%)	54 (17%)
CD4 count (cells per μL)	443 (299, 590)	450 (324, 608)	440 (289, 591)	441 (297, 597)
Number with CD4 cell count (cells per μL)				
<200	36 (11%)	32 (10%)	44 (14%)	34 (10%)
≥200 to <500	156 (50%)	149 (47%)	158 (49%)	171 (53%)

Characteristic	Study 1489		Study 1490	
	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	Dolutegravir, abacavir, and lamivudine (n=315)	Bictegravir, emtricitabine, and tenofovir alafenamide (n=320)	Dolutegravir plus emtricitabine, and tenofovir alafenamide (n=325)
≥500	122 (39%)	134 (43%)	118 (37%)	120 (37%)
Creatinine clearance by Cockcroft-Gault formula (mL/min)	125.9 (107.7, 146.3)	123.0 (107.0, 144.3)	120.4 (100.8, 141.8)	120.6 (102.8, 145.1)
Body-mass index (kg/m^2)	25.1 (22.4, 28.7)	24.9 (22.5, 29.1)	25.0 (22.2, 28.3)	24.6 (22.2, 28.0)
Primary resistance-associated mutations[b]				
INSTI	4 (1.3%)	4 (1.3%)	3 (1%)	6 (2%)
NRTI	6 (1.9%)	5 (1.6%)	10 (3%)	5 (2%)
NNRTI	36 (11.5%)	51 (16.2%)	41 (13%)	41 (13%)
PI	12 (3.8%)	11 (3.5%)	4 (1%)	10 (3%)
HIV/HBV Coinfected			8 (3%)	6 (2%)
HIV/HCV Coinfected			5 (2%)	5 (2%)

Data are median (IQR) or n (%), except for age, which is median (range).
INSTI = integrase strand transfer inhibitor; IQR, interquartile range; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor
a A participant may fit more than one HIV risk factor category; therefore, percentages may add to more than 100%.
b Primary INSTI substitutions are Thr66Ala/Ile/Lys, Glu92Gly/Gln, Thr97Ala, Phe121Tyr, Tyr143Cys/His/Arg, Ser147Gly, Gln148His/Lys/Arg, Asn155His/Ser, Arg263Lys in IN. Primary NRTI substitutions are Met41Leu, Lys65Glu/Asn/Arg, Asp67Asn, Thr69 insertions, Lys70Glu/Arg, Leu74Ile/Val, Tyr115Phe, Gln151Met, Met184Val/Ile, Leu210Trp, Thr215Tyr/Phe, Lys219Glu/Asn/Gln/Arg in RT. Primary NNRTI substitutions are Leu100Ile, Lys101Glu/Pro, Lys103Asn/Ser, Val106Ala/Met, Val108Ile, Glu138Ala/Gly/Lys/Gln/Arg, Val179Leu, Tyr181Cys/Ile/Val, Tyr188Cys/Leu/His, Gly190Ala/Glu/Gln/Ser, His221Tyr, Pro225His, Phe227Cys, Met230Ile/Leu in RT. Primary PI substitutions are Asp30Asn, Val32Ile, Met46Ile/Leu, Ile47Ala/Val, Gly48Val, Ile50Val/Leu, Ile54Leu/Met, Gln58Glu, Thr74Pro, Leu76Val, Val82Ala/Phe/Leu/Thr/Ser, Asn83Asp, Ile84Val, Asn88Ser, Leu90Met in PR.

Table 2. Virologic outcomes at week 144

	Study 1489		Study 1490	
	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	**Dolutegravir, abacavir, and lamivudine (n=315)**	**Bictegravir, emtricitabine, and tenofovir alafenamide (n=320)**	**Dolutegravir plus emtricitabine, and tenofovir alafenamide (n=325)**
HIV-1 RNA <50 copies per mL (full analysis set)	256 (81.5%)	265 (84.1%)	262 (81.9%)	273 (84.0%)
Difference in Percentages (95% CI)†	-2.6% (-8.5% to 3.4%)		-1.9% (-7.8% to 3.9%)	
HIV-1 RNA ≥50 copies per mL	2 (0.6%)	9 (2.9%)	15 (4.7%)	10 (3.1%)
HIV-1 RNA ≥50 copies per mL	1 (0.3%)	2 (0.6%)	1 (0.3%)	4 (1.2%)
Discontinued Due to Lack of Efficacy	0	0	0	0
Discontinued Due to Other Reasons* and Last Available HIV-1 RNA ≥50 copies per mL	1 (0.3%)	7 (0.6%)	14 (4.4%)	6 (1.8%)
No Virologic Data	56 (17.8%)	41 (13.0%)	43 (13.4%)	42 (12.9%)
Discontinued Due to AE/Death¥	2 (0.6%)	6 (1.9%)	8 (2.5%)	9 (2.8%)
Discontinued Due to Other Reasons* and Last Available HIV-1 RNA <50 copies per mL	50 (15.9%)	34 (10.8%)	35 (10.9%)	29 (8.9%)
Missing Data but on Study Drug	4 (1.3%)	1 (0.3%)	0	4 (1.2%)
HIV-1 RNA <50 copies per mL (per-protocol set)	256/257 (99.6%)	260/262 (99.2%)	257/258 (99.6%)	270/273 (98.9%)
Difference in Percentages (95% CI)†	0.4% (-1.6% to 2.4%)		0.7% (-1.4% to 2.7%)	
HIV-1 RNA <50 copies per mL by Missing = Failure	259/314 (82.5%)	267/315 (84.8%)	268/320 (83.8%)	276/325 (84.9%)
Difference in Percentages (95% CI)**	-2.3% (-8.1% to 3.6%)		-0.9% (-6.6% to 4.7%)	
HIV-1 RNA <50 copies per mL by Missing = Excluded	259/260 (99.6%)	267/269 (99.3%)	268/270 (99.3%)	276/280 (98.6%)
Difference in Percentages (95% CI)**	0.4% (-1.6% to 2.3%)		0.7% (-1.6% to 2.9%)	
HIV-1 RNA <20 copies per mL (full analysis set)	245 (78.0%)	259 (82.2%)	248 (77.5%)	257 (79.1%)
Difference in Percentages (95% CI)†	-4.2% (-10.5% to 2.1%)		-1.1% (-7.4% to 5.3%)	

Data are n (%).
The Week 144 window is between Days 967 and 1050 (inclusive).
*Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
† The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum and region stratum¥ One death in the bictegravir, emtricitabine, and tenofovir alafenamide occurred after the participant reached the week 96 outcome.

** Difference in percentages, and 95% CI were based on a dichotomized response: HIV-1 RNA <50 copies/mL vs. HIV-1 RNA ≥ 50 copies/mL or missing for missing = failure approach and HIV-1 RNA <50 copies/mL vs. HIV-1 RNA ≥ 50 copies/mL for missing = excluded approach. Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum and region stratum.

Table 3. Adverse events through week 144

	Study 1489			Study 1490		
	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	**Dolutegravir, abacavir, and lamivudine (n=315)**	**p-value¥**	**Bictegravir, emtricitabine, and tenofovir alafenamide (n=320)**	**Dolutegravir plus emtricitabine, and tenofovir alafenamide (n=325)**	**p-value¥**
Any adverse event	300 (95.5%)	304 (96.5%)	—	291 (90.9%) 3	300 (92.3%)	—
Adverse event ≥10%						
Nausea	38 (12.1%)	76 (24.1%)	0.0001	31 (9.7%)	42 (12.9%)	—
Diarrhoea	54 (17.2%)	57 (18.1%)	—	66 (20.6%)	52 (16.0%)	—
Upper respiratory tract infection	43 (13.7%)	59 (18.7%)	—	43 (13.4%)	52 (16.0%)	—
Headache	44 (14.0%)	56 (17.8%)	—	56 (17.5%)	57 (17.5%)	—
Nasopharyngitis	40 (12.7%)	52 (16.5%)	—	50 (15.6%)	62 (19.1%)	—
Syphilis	39 (12.4%)	49 (15.6%)	—	33 (10.3%)	31 (9.5%)	—
Back pain	34 (10.8%)	38 (12.1%)	—	28 (8.8%)	38 (11.7%)	—
Fatigue	33 (10.5%))	38 (12.1%	—	28 (8.8%)	36 (11.1%)	—
Insomnia	25 (8.0%)	35 (11.1%)	—	29 (9.1%)	24 (7.4%)	—
Oropharyngeal pain	21 (6.7%)	35 (11.1%)	—	20 (6.3%)	18 (5.5%)	—
Cough	34 (10.8%)	20 (6.3%)	—	25 (7.8%)	29 (8.9%)	—
Grade 3 or 4 adverse event	50 (15.9%)	50 (15.9%)	—	54 (16.9%)	43 (13.2%)	—
Serious adverse event	41 (13.1%)	53 (16.8%)	—	63 (19.7%)	40 (12.3%)	—
Study drug-related adverse event	94 (29.9%)	132 (41.9%)	0.0021	71 (22.2%)	95 (29.2%)	—
Study drug-related adverse event ≥5%						
Nausea	18 (5.7%)	56 (17.8%)	<0.0001	10 (3.1%)	17 (5.2%)	—
Diarrhoea	19 (6.1%)	13 (4.1%)	—	10 (3.1%)	10 (3.1%)	—
Headache	16 (5.1%)	16 (5.1%)	—	14 (4.4%)	10 (3.1%)	—
Study drug-related serious adverse event	2 (0.6%)	1 (0.3%)	—	3 (0.9%)	3 (0.9%)	—

	Study 1489			Study 1490		
	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	**Dolutegravir, abacavir, and lamivudine (n=315)**	**p-value¥**	**Bictegravir, emtricitabine, and tenofovir alafenamide (n=320)**	**Dolutegravir plus emtricitabine, and tenofovir alafenamide (n=325)**	**p-value¥**
Any adverse event leading to study drug discontinuation*	0	5 (1.6%)	—	6 (1.9%)	6 (1.8%)	—
Death†	2 (0.6%)	1 (0.3%)	—	4 (1.3%)	4 (1.2%)	—

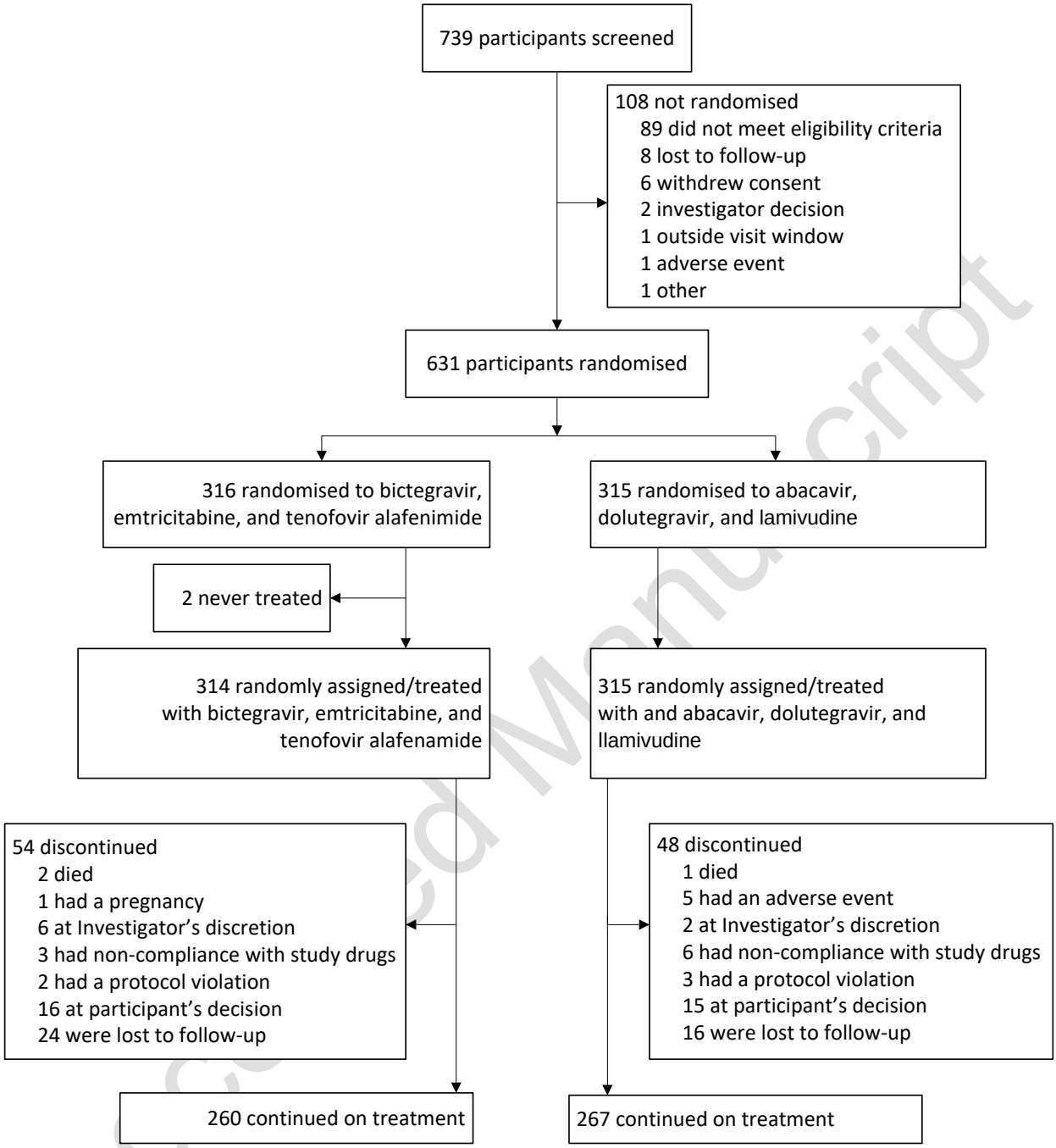
Data are n (%).

¥ Significance testing was performed for events with >5% treatment difference. P-values were calculated using Fisher exact text.

* In Study 1489, adverse event-related study drug discontinuations in the dolutegravir, abacavir, and lamivudine group included nausea and rash generalized (day 4, n=1); thrombocytopenia (day 50, n=1); chronic pancreatitis and steatorrhoea (day 134, n=1); depression (day 248, n=1); and renal failure (day 621, n=1).

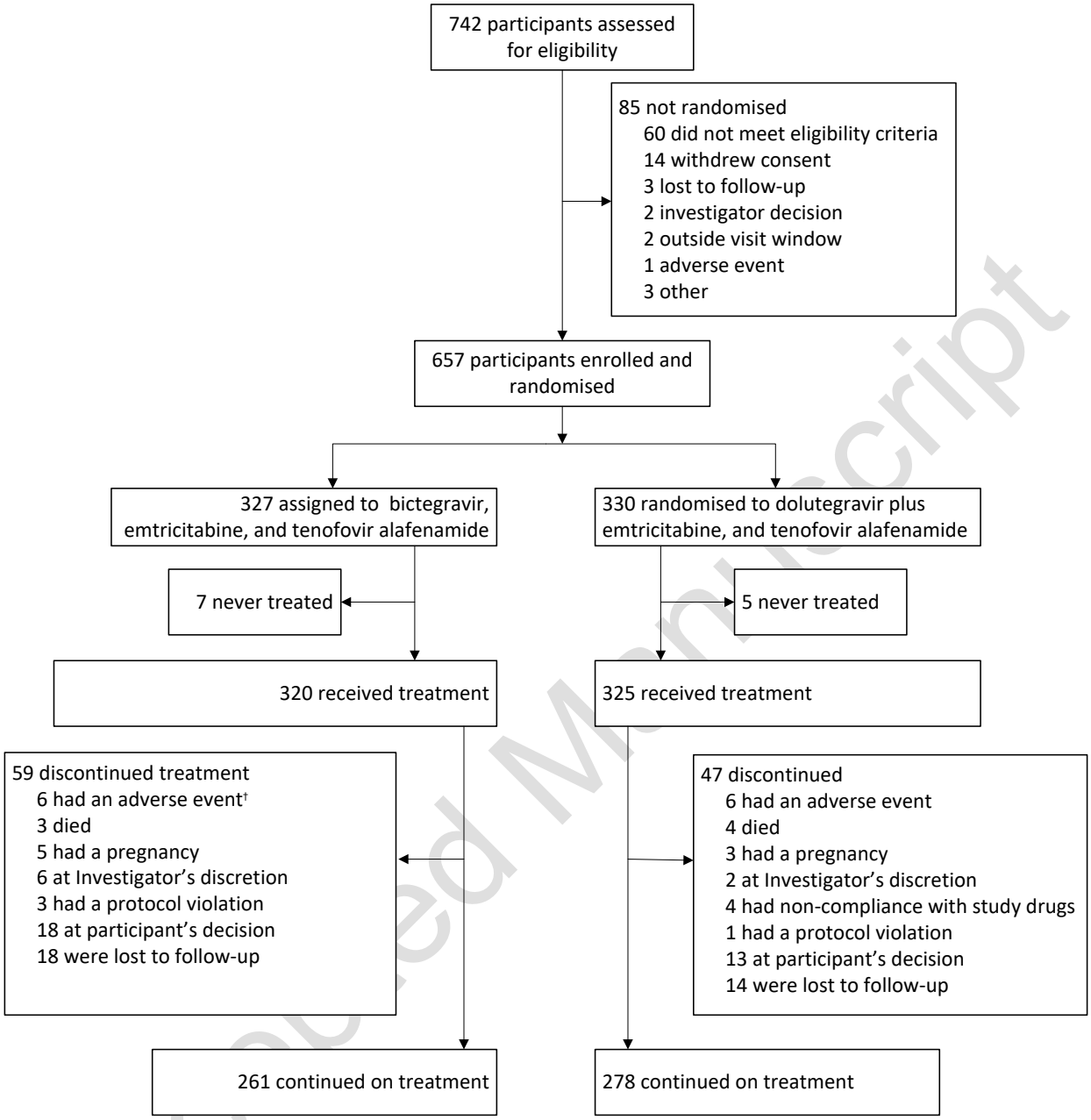
† In Study 1489, deaths in the bictegravir, emtricitabine, and tenofovir alafenamide group included recreational drug overdose (day 771, n=1) and suicide (day 656, n=1); neither event was considered to be treatment related. The death in the dolutegravir, abacavir, and lamivudine group was recreational drug overdose (day 812, n=1); this event was not considered to be treatment related. In Study 1490, deaths in the bictegravir, emtricitabine, and tenofovir alafenamide group included cardiac arrest following appendicitis and septic shock (day 28, n=1), gastric adenocarcinoma (day 376, n=1), hypertensive heart disease and congestive heart failure (Day 412, n=1), and sudden cardiac death (day 1060, n=1). Deaths in the dolutegravir plus emtricitabine and tenofovir alafenamide group included unknown causes (day 174, n=1; day 771, n=1), pulmonary embolism (day 266, n=1), and lymphoma (day 422, n=1). None of the deaths in either study were considered to be treatment related.

Figure 1. Study 1489: study profile through week 144



AE, adverse event; B/F/TAF, bictegravir, emtricitabine, and tenofovir alafenamide; D/C, discontinuation; DTG/ABC/3TC, dolutegravir, abacavir, lamivudine

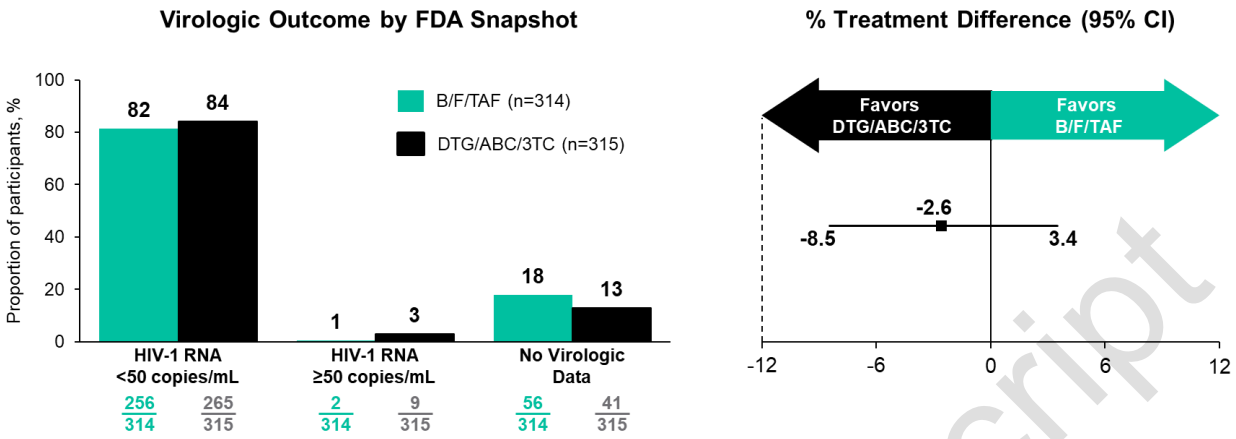
Figure 2. Study 1490: study profile through week 144



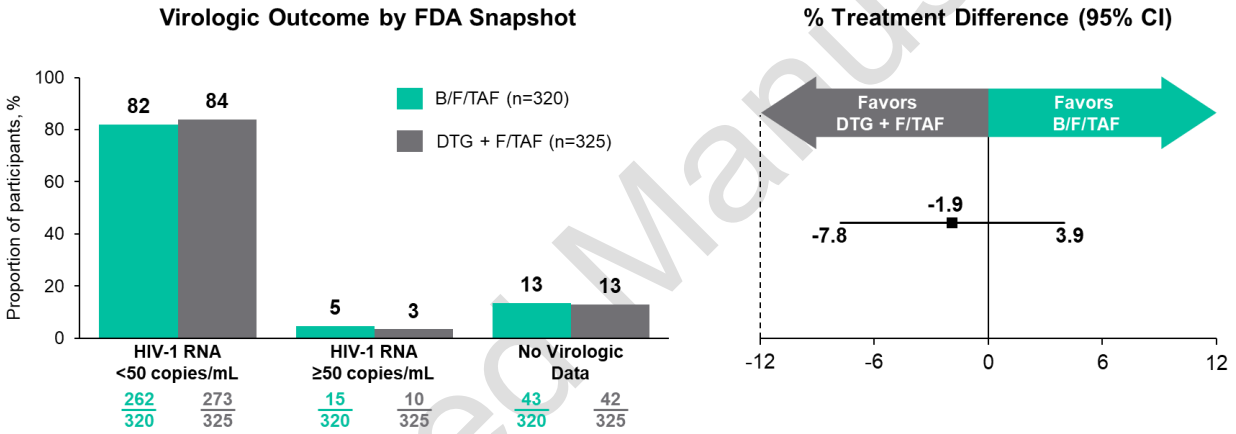
No participants discontinued treatment due to reasons related to efficacy. *One participant who discontinued because of an adverse event had a cardiac arrest (following appendicitis and septic shock) and died.

Figure 3. Virologic outcome at week 144

A) Study 1489



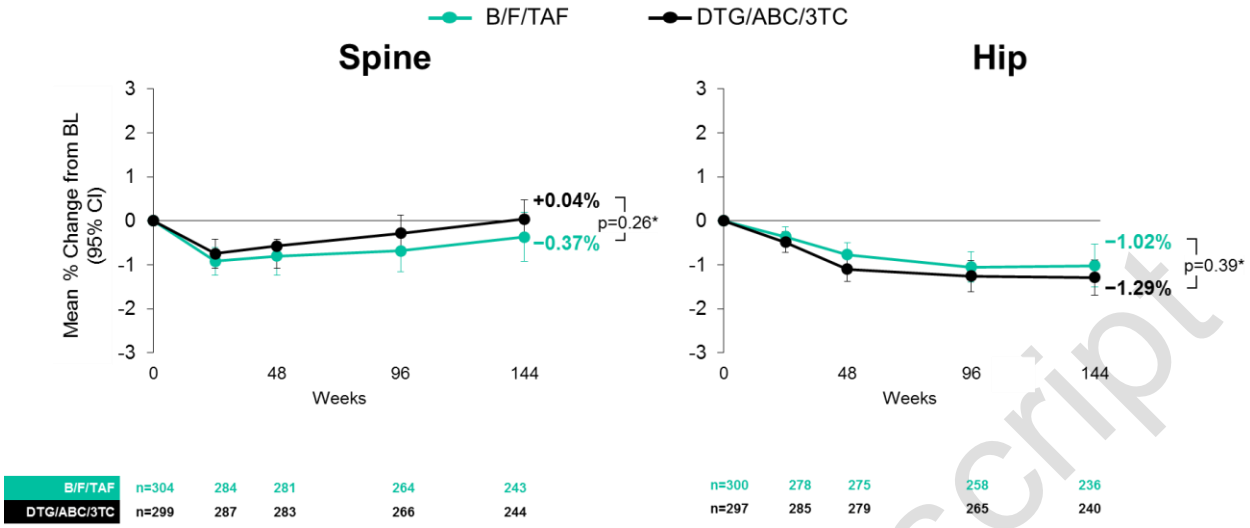
B) Study 1490



% treatment difference was adjusted for both studies.

B/F/TAF, bictegravir, emtricitabine, and tenofovir alafenamide; CI, confidence interval; DTG/ABC/3TC, dolutegravir, abacavir, lamivudine; FAS, full analysis set

Figure 4. Mean (95% CI) percent change from baseline at weeks 24, 48, 96, and 144 in lumbar spine and hip BMD by DXA (Study 1489)



B/F/TAF = bictegravir, emtricitabine, and tenofovir alafenamide
DTG/ABC/3TC = dolutegravir, abacavir, and lamivudine
BMD = bone mineral density
Bars show 95% CI.